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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/793,653	02/27/1997	FREDERIC DE SAUVAGE	GTEC113469	5602

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	17

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/793,653	DE SAUVAGE ET AL.	
	Examiner	Art Unit	
	Zachary C Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 1998*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-26 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3-25-03,6-10-02,3-13-01, 4-17-00, and 12/3/1998*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Ex parte prosecution was suspended due to a potential interference in the papers. Prosecution is now re-opened. New Grounds of Rejection are set forth herein.

2. Claims 13-26 and 28 are under consideration in the instant application.

3. This Office Action will be in response to applicant's arguments, filed 12-03-98. Applicant's arguments have been fully considered but they are not persuasive. It is believed all pertinent arguments have been addressed. The rejections of record can be found in the previous Office Action. Any objections, rejections, and/or concerns not herein restated are withdrawn.

4. The following documents were not available to the examiner at the time of examination:

Documents listed on the Information Disclosure Statement filed 3/13/2001, paper number 14, documents numbered 10-21 (WO94/11404; WO95/21864; WO 96/31526; WO 97/12037; WO 97/26335; Baumann et al 1996; Bennett et al 1996; Burguera et al 2000; Chua Jr et al 1996; Hoggard et al 2000; Luoh et al 1997; and Francis 1997),

Documents listed on the Information Disclosure Statement filed 4/17/2000, paper number 12, documents numbered WO97/48419, WO97/48806, WO98/28427, EP0956862A1, EP0396387A2, EP0396387A3, WO91/01004, WO96/34885A2, WO96/34885A3, WO/9623517, WO96/24670, WO97/00319, PCT/CG9601388, EP0741187A2, and Hollenbaugh et al.

Applicants may, in response to this and no later Office Action, submit the missing references. Such submissions will be considered to have been part of the respective Information Disclosure Statement filed on 2/27/1997, and the PTO-1449 will be updated accordingly. No fee for the submission of such references is required, nor should applicants file an additional form PTO-1449 with the missing references.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treatment of obesity, or type II diabetes, does not reasonably provide enablement for methods of treatment of type I diabetes, or bulimia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of treatment of type I diabetes, or bulimia, associated with the abnormal expression or function of the OB gene comprising administration to a patient a therapeutically effective amount of the chimeric polypeptide comprising the native OB protein fused to an immunoglobulin heavy chain constant domain.

As noted in the specification (page 1, lines 14-15) the prior art teaches that an "*ob*" single-gene mutation results in obesity and type II diabetes in mice. Therefore, type II diabetes is associated with the abnormal expression of the OB gene. In contrast, the prior art teaches that type I diabetes "is not associated with obesity" (Ganong, 1989.

Review of Medical Physiology, pages 299-300). Similarly, the art teaches in a bulimic patient, "although binging and purging episodes were quite frequent, leptin levels remained stable and were neither related to food intake nor to binge episodes" (Abstract of Herpetz et al, May 1998 May; 23(4): 459-653), and "although bulimic patients have very bad nutritional behavior, their leptin levels do not appear altered" (Abstract of Calandra, et al, June 2003; 8(2): 130-7). To date, the art has not established a connection abnormal expression of the OB gene and type I diabetes, or bulimia.

The specification does not provide sufficient guidance to practice the claimed invention without undue experimentation. The specification teaches (page 1, lines 11-13) "Obesity is responsible for a variety of serious health problems, including cardiovascular disorders, type II diabetes, insulin-resistance, hypertension, hypertriglyceridemia, dyslipoproteinemia, and some forms of cancer." However, nowhere does the specification teach that type I diabetes or bulimia is related to obesity, or to an association with the abnormal expression or function of the OB gene. The nexus between type I diabetes, or bulimia, and obesity or abnormal expression or function of the OB gene is nowhere established. A person of skill in the art would have no expectation of the success of treatment of type I diabetes, or bulimia, with an Ob-Ig fusion protein due to the lack of this nexus.

The quantity of experimentation needed to make and use the invention as claimed would be undue because a person of skill in the art would need to confirm a nexus between type I diabetes, or bulimia, and abnormal expression or function of the OB gene, and test whether administration of an OB-Ig fusion protein would treat the condition of type I diabetes, or bulimia.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 13 and 15, which merit priority to 12/27/1995, are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Pellymounter, US Patent Application Publication No. 2003/0203837, filed 5/30/2003 but meriting priority to 11/22/1995.

Pellymounter teaches (paragraph 31) "Fusion proteins may be prepared by attaching polyaminoacids to the OB protein (or analog) moiety. For example, the polyamino acid may be a carrier protein which serves to increase the circulation half-life of the protein. Such polyamino acid may be selected from the group consisting of ...an antibody or portion thereof (such as an antibody constant region, sometimes called "Fc").... As indicated below, the location of attachment of the polyamino acid may be at the N-terminus of the OB protein moiety, or other place, and also may be connected by a chemical "linker" moiety to the OB protein." The term Fc refers to a part of the antibody consisting of only heavy chain constant domain sequences. Pellymounter teaches (paragraph 16, lines 1-2) that the OB protein used may be the human OB protein according to Zhang et al (Reference 37 of the IDS filed 12-3-1998). The sequence taught by Zhang in Figure 6b (page 430) is "sequence of human ob protein" and includes an initiating N-terminal methionine. Pellymounter, in claim 1, teaches "A fusion protein optionally having an N-terminal methionine comprising an

antibody constant region or portion thereof attached to the N-terminus of an OB protein." Therefore, Pellymounter teaches all of the limitations of claims 13 and 15 of the current invention, including a native OB protein, with or without an initiating N-terminal methionine, fused to immunoglobulin heavy chain sequence, and that the OB protein is human.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-26 and 28, stand rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Zhang et al, Basinski et al ('744 or '886), DiMarchi et al ('954 or '336), in view of Shin et al, or Ashkenazi et al.

Applicant's arguments, filed 12/03/1998, have been fully considered but have not been found persuasive.

This rejection is maintained for the reasons of record. The full rejection of record may be found in Paper No. 3, filed 5/27/1998.

Applicant concedes that native OB proteins, and broad teachings for making receptor-immunoglobulin fusions (immunoadhesins), were known in the art at the priority date of the present application. Applicants submits that the specific OB protein-immunoadhesins (OB-Ig) of the present invention are patentable over the cited combination of references in view of their unexpected properties. However, there is insufficient evidence of record to establish unexpected results. The alleged unexpected

results applicants point out, are that the OB-Ig chimera is more potent at reducing body weight and adipose tissue deposits relative to a native human OB protein lacking Ig. However, the secondary references cited to show protein-Ig chimeras, their preparation, and the advantages for the preparation and use of such, teach that the fusion of the Ig to various proteins would result in improvements in activity as well as delivery and bioavailability. Thus, the results that applicants may have obtained are not "unexpected", but rather what the art would have expected.

Further, applicants argue that at the priority date of the application, the receptor of the OB protein had not been identified, and submits references that at least one biologically significant receptor was localized in the brain. Applicants submit that the present invention is unexpected because the prior referenced art suggested the biologically relevant OB receptor is located in the brain, and the OB-Ig chimera would not be expected to be able to cross the blood-brain barrier. The fact that earlier OB protein studies may not have fully recognized the nature of the interaction of the protein with its cognate receptor, and where such receptors were located, does not detract from the obviousness. The art had not determined that the OB receptor was located exclusively in the brain, and the isolation of the OB protein from other cells and tissues would have suggested to the person of ordinary skill in the art that the OB receptor was also located in these cells and tissues, since it was presumed that the OB protein acted via its cognate receptor. The fact that applicants believe that the molecular weight of the OB-Ig chimera should prevent it from crossing the blood-brain barrier also does not detract from the obviousness, both because of the above comments about the different cellular sources for the protein and the receptor, and because the secondary reference

had taught that Ig could be fused to other proteins that had a MW in excess of the OB protein. Further, it was known in the art at the time the invention was made that transferrin-Ig fusions could penetrate the blood brain barrier more effectively than native transferrin despite a large molecular weight (see the first paragraph of the Discussion, page 2823, Shin, et al #2, 1995, PNAS, 92:2820-2824). Accordingly, the art does not support applicant's allegation that the Ig fusion would not be expected to cross the blood-brain barrier, nor is such required for the prima facie finding of obviousness.

Applicants' amendments to claims 13, 14, 18, 21, and 22 do not overcome the prima facie finding of obviousness. All of the limitations of the amended claims are taught by the primary and secondary references, and the motivation to combine these references is obvious for the reasons of record. Applicant amended the indicated claims to read on a native OB protein with or without an N-terminal methionine, and with or without the native signal sequence fused to an immunoglobulin heavy chain constant domain sequence comprising the hinge, CH2 and CH3 regions of an IgG. The primary reference Zhang teaches (page 429, column 2) native OB with or without a native signal sequence: "...about half of the ob primary translation product was truncated by ~2K, in the presence of microsomal membranes, which suggests that the signal sequence is functional (Fig. 4c)." An Ob protein with or without the native signal sequence inherently corresponds to a protein with or without the initiating N-terminal methionine. The secondary reference Ashkenazi teaches (page 104, column 2) fusions linked to the "the hinge, CH2, and CH3 domains of human IgG heavy chain...we will use this immunoadhesin structure as a prototype." Thus, the primary and secondary references

teach all of the further limitations introduced by amendment, and the claims remain obvious for reasons of record.

Claim 28, added by amendment 12-03-1998, is rejected for the same reasons of record as claims 13-26.

It is believed that all pertinent arguments have been addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:00 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Lorraine Spector

LORRAINE SPECTOR
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